NAVAL HEALTH RESEARCH CENTER

NEUROTICISM AND ANTIBODY RESPONSES IN MILITARY RECRUITS

R. R. Vickers, Jr.

L. K. Hervig

Report No. 91-47

NAVAL HEALTH RESEARCH CENTER
P. O. BOX 85122
SAN DIEGO, CALIFORNIA 92186 – 5122

NAVAL MEDICAL RESEARCH AND DEVELOPMENT COMMAND
BETHESDA, MARYLAND

NEUROTICISM AND ANTIBODY RESPONSES IN MILITARY RECRUITS

Ross R. Vickers, Jr.

Linda K. Hervig

Cognitive Performance and Psychophysiology Department

Naval Health Research Center

P.O. Box 85122

San Diego, CA 92186-5122

Ruth Rappaport

Paul Linard

Wyeth-Ayerst Laboratories

P.O. Box 304

Marietta, PA 17547

*Technical Report 91-47 supported by the Naval Medical Research and Development Command, Bureau of Medicine and Surgery, Department of the Navy, under Research Work Unit MR04101.00A-6004. The views presented are those of the authors and do not reflect the official policy of the Department of the Navy, Department of Defense, nor the U.S. Government.

Summary

Problem

Research with animals suggests that inoculations given to protect against viruses may be ineffective when given during periods of high stress because stress-related down-regulation of the immune system impairs the immune response to vaccination.

Objective

This study was undertaken to quantify the effects of stress on antibody production in U.S. Navy recruits. The estimates were developed by comparing the antibody production of stress-susceptible recruits to that of stress-resistant recruits following routine inoculations during the challenging initial phases of training.

Approach

The 12 highest and 12 lowest scorers on a measure of emotionality and stress-susceptibility were selected from a larger sample. The neutralizing antibody responses to inoculations for adenovirsuses 4 and 7 given the day of arrival at the Recruit Training Command, San Diego, were determined two days after inoculation, then 23-25 days later, then again another 24-27 days later.

Results

Most recruits had detectable antibody levels two days after inoculation (91.8% for adenovirus 7; 58.4% for adenvirus 4). Among recruits with detectable antibodies two days after inoculation, stress-susceptible recruits had lower antibodies than stress-resistant recruits for both adenoviruses at the time of the first antibody measurement, but not for the two later measurements.

Conclusions

Antibody responses to booster shots may be sluggish in stress-susceptible individuals if given at a stressful time. This information suggests that it is desirable to allow sufficient time between inoculation and deployment to permit even stress-susceptible individuals to respond to booster shots given as part of preparations for deployment or other instances of potential exposures to important viruses. Additional studies to define the precise time course of antibody responses and determine whether the results generalize to initial inoculations and to other viral and bacterial pathogens would be useful for establishing vaccination policies.

Introduction

Psychoimmunological models are attracting increasing attention as scientifically viable representations of disease-related processes. The evidence for such models includes associations between immune function and personality (Jemmott & Locke, 1984; O'Leary, 1990). Antibody responses to pathogens are of interest in relation to such models because these responses require the coordinated action of immune system components over extended time periods (Roitt, Brostoff, & Male, 1985). Antibody responses, therefore, have the potential to provide an index of the integrated impact of any psychological effects on specific components of the immune system across time and specific immune subsystems. Antibody responses have been sensitive to stress in animal models, including murine (Laudenslager et al., 1988) and primate (Coe, Rosenberg, Rischer, & Levine, 1987) models. However, early studies of humans have produced generally negative results (Greene, Betts, Ochitill, Iker, & Douglas, 1978; Locke & Heisel, 1977). A recent study by Glaser et al. (1992) showed that seroconversion to Hepatitis B vaccine was delayed in medical students who reported relatively high stress and anxiety at the time of the initial inoculation.

Although the general pattern of results from animals and humans suggests that stress can delay antibody responses to inoculations, there is limited evidence available to support this assertion as it applied to humans. Any generalization from animal models to humans must be made cautiously, so the apparent inconsistency between earlier findings and Glaser et al.'s (1992) recent results is a concern until further evidence is available on this topic. The present study provides further evidence by describing antibody responses to adenovirus inoculations in military recruits using a study design that is qualitatively similar to Glaser et al.'s (1992) work.

Study design differences may account for the apparent inconsistency of findings when moving from the animal to the human literature on stress and antibody production. Human studies typically involve less control over the type of stress, the timing of stress relative to the introduction of antigens, and study participants' prior history of exposure to the antigen than is possible in animal studies. In Locke and Heisel's (1977) study, prior exposure was evaluated by determining antibody levels prior to inoculation, and stress was assessed in terms of life change events. Life change stress measures cumulate a variety of events over periods of a month to a year. As a result, such measures do not provide well-defined controls for the type and timing

of stress relative to the inoculation. Greene et al. (1978) isolated subjects during their study, but no acute stress was imposed except the incidental effects of being confined voluntarily to a motel for a 7-day period. Instead, stress again was measured by recent life changes. Thus, animal model results may replicate in humans when key aspects of the study conditions that apply to animals also apply to the humans. In the Locke and Heisel (1977) study, the lack of control over differences in living conditions during the study also may have affected the results.

The study design employed by Glaser et al. (1992) involved conditions which were more standardized across study participants. The timing of stress was fixed relative to the inoculations by giving the shots at fixed times prior to medical school examinations. Prior research by Glaser and his colleagues has established that these examinations reliably produce higher reports of stress and changes in various aspects of immune function. Although student's lives are not directly controlled by the investigators, the fact that the study participants attend the same classes and must prepare for the same tests implies some degree of standardization. These aspects of the Glaser et al. (1992) study design may have had an important influence on the results of their study.

The present investigation evaluated antibody responses in humans under conditions that approximated the controlled conditions typical in animal studies and attributed above to the Glaser et al. (1992) study. This study tested the hypothesis that individual differences in neuroticism would be related to primary antibody responses to inoculations for adenoviruses 4 and 7 given to military recruits at a stressful point in basic training. The adenovirus inoculations that provided the challenge to the immune system are given routinely to all recruits the day of arrival at basic training. Previous serological surveys have indicated that most recruits could be expected to have had no prior exposure to these viruses prior to arrival at basic training (Foy & Grayston, 1982). These findings gave reason to believe that it would be possible to examine the primary antibody response to these inoculations. This assumption was tested by including a measure of antibody levels two days after the inoculations as a means of detecting anamnestic antibody responses in any individuals who had prior exposure with the intent of dropping them from subsequent analyses.

Extensive previous research on the structure and nature of military basic training gave reason to believe that the research design would permit an assessment of antibody responses

during a period of relatively standardized psychological stress under controlled living conditions. Observers agree that basic training requirements confront recruits with a series of adaptive challenges (Bourne, 1967; Janis, 1945; Maskin & Altman, 1943; Zurcher, 1968), thereby satisfying at least one definition of stress (Lazarus & Folkman, 1984). Basic training is a novel situation for nearly all recruits that reliably produces a peak of negative affect early in training (Datel & Engle, 1966; Datel, Engle, & Barba, 1966; LaRocco, Ryman, & Biersner, 1977). During this period, the living and working conditions of recruits are standardized by a fixed training program, including physical training, barracks living quarters, and mess hall food.

The effect of stress on antibody response could not be directly observed in this study because all recruits were exposed to the demands of basic training. No suitable control group which was receiving the inoculations was available for study. However, current stress models emphasize that exposure to a stressful event probably is less important than the individual's evaluation of that event in defining the psychological processes that define stress as experienced by the person (Lazarus & Folkman, 1984). As a result, the standardized events of basic training could produce very different levels of stress in different individuals, depending on their perceptions of training.

In the present study, individual differences in neuroticism were used to define groups that were expected to differ with regard to subjective stress. One reason was that neuroticism includes stress vulnerability as one element (Costa & McCrae, 1985), so neurotics should feel more stress than emotionally-stable individuals, all other things equal. In addition, neuroticism is a well-established correlate of emotional reactions to many types of life events, and emotional reactions may be the key step in transforming psychosocial stresses into adverse health outcomes (Thoits, 1984).

There is evidence that neurotic tendencies are activated by the challenges of basic training. In recruit training, high scores on neuroticism are related to a lower probability of success in training (see Hough, 1988, for a review), more negative affect (Vickers, Kusulas, & Hervig, in preparation), less adaptive coping (Vickers, Kolar, & Hervig, 1989), higher cortisol secretion and excretion (Rose, Poe, & Mason, 1968; Vickers, Hervig, Wallick, Poland, & Rubin, 1987), lower levels of natural killer cell activity (Vickers, Hervig, Levy, Herberman, & Whiteside, in preparation), and more severe illness (Vickers & Hervig, 1988b; Voors, Rytel, Jenkins, Pierce,

& Stewart, 1969). Cumulatively, this range of behavioral, psychological, and biological correlates of neuroticism in basic training implies that neuroticism is an important aspect of personality in any psychobiological model of adaptation to military basic training. Based on the prior results which suggest higher stress among neurotic individuals, the present study tested the hypothesis that the antibody response to the adenovirus inoculations would be lower among neurotic recruits than among emotionally-stable recruits.

Method

Sample

The sample consisted of 24 male U.S. Navy recruits who volunteered to participate in a study of risk factors for infectious disease in basic training. The typical recruit in the sample was an 18.5 (S.D. = 1.5, range = 17 - 24) year old Caucasian (96%, 1 participant was Asian) with a high school diploma (96%).

This sample was composed of the recruits with the 12 highest and lowest neuroticism scores in a sample of 137 recruits who participated in this study. The selection of extreme groups increased the variance in neuroticism relative to the overall population. This increase will magnify associations between neuroticism and other variables, thereby making it easier to detect these associations when applying standard statistical tests (Hunter, Schmidt, & Jackson, 1982). This increase in sensitivity was considered desirable given the preliminary nature of the study and the likelihood that effect sizes would be in the small to moderate range (Cohen, 1969). The alternative approach of increasing the sample size was not feasible because the viral assays used were so complex and time consuming. Because the estimates of associations are biased, both raw effect size estimates and effect size estimates incorporating correction for enhancement of range (Hunter et al., 1982) are reported where the effects of selection on the variances of the study variables can be estimated.

Neuroticism Measure

The NEO Personality Inventory (Costa & McCrae, 1985) was administered the day recruits began basic training. The neuroticism measure from this inventory is a 48-item scale comprised of 8 items each to measure anxiety, depression, anger, self-consciousness (or social anxiety), vulnerability to stress, and impulsiveness as specific components or facets of this

general dimension. Cronbach's alpha for the overall neuroticism scale was .91 in a sample of 360 adult males (Costa & McCrae, 1985). In the U.S. Navy recruit population, Cronbach's alpha was .90 (n = 2,957). Individual differences in scores on this neuroticism scale are stable over time (r = .83 over six years; Costa & McCrae, 1988) and correlate strongly with other measures of neuroticism (e.g., r = .75 with Eysenck neuroticism scale; McCrae & Costa, 1985).

As noted above, the sample was comprised of recruits who were in the top or bottom 9% of those participating in the research protocol. These groups are referred to in this paper as "neurotic" and "emotionally-stable," respectively. These categorical labels have been applied to simplify the presentation and discussion of results, but it is important to remember that the neuroticism scale measures individual differences falling within the normal range of neurotic tendencies. For this reason, the use of the designation "neurotic" in this paper does not necessarily correspond to the use of this term to designate significant personality disorders.

The use of extreme groups coupled with established characteristics of the neuroticism scale helps minimize some potential interpretive issues when considering the results. Given the estimated measurement precision of the scale, the extreme selection criteria made it unlikely that any individual was misclassified with respect to group membership. Combined with the known temporal stability of the neuroticism scores, the selection criteria made it unlikely that any recruit's group designation would change during the short period of basic training. Combined with available evidence of convergent validity with other standardized measures of neuroticism (cf., Costa & McCrae, 1985), the selection criteria made it highly probable that any recruit designated neurotic or emotionally-stable would have met typical criteria for the same classification (e.g., a median split) if some other inventory had been substituted for the NEO Personality Inventory.

Illness Measures

Illness during basic training was measured by symptom complaints obtained at weekly intervals during basic training. At each data collection session, recruits completed a symptom check list by indicating the severity of an extensive series of symptoms using a 5-point Likert scale with response options ranging from "Not experienced" to "Extremely Severe." The primary illness measure was an 8-item upper respiratory illness composite which consisted of severity ratings for complaints of fever, sore throat, productive cough, nonproductive cough, stuffy nose,

hoarseness, sinus pain, and sneezing. In addition, symptom composites were computed for musculoskeletal complaints (muscle aches, aching joints and bones, muscle cramps) and for miscellaneous symptom reporting (skin irritation, diarrhea, vomiting, trouble hearing). Musculoskeletal complaints and miscellaneous symptom reporting were scored by taking the average of the severity ratings for the indicated symptoms, but total URI score was adjusted for concurrent complaints of allergy and injury. The rationale behind these procedures, and the empirical development of the scales is described in Vickers and Hervig (1988a). The musculoskeletal complaints and miscellaneous symptom reporting were included to determine whether any significant associations between URI and the other variables studied were unique to URI or represented general associations to a range of symptoms.

Measures of overall illness experiences during the period of study were obtained by taking the cumulative illness reports for the second through fourth weeks of the study. The reports from the first week were excluded on the basis of prior evidence that these reports are more contaminated by psychological reactions to stress than are reports obtained later in training (Vickers & Hervig, 1988a).

Antibody Assay Procedures

Recruits are inoculated with a live oral vaccine the day they arrive at the Recruit Training Command. The initial blood sample was drawn two days later. The second blood sample was drawn 23 to 25 days after that, and the final blood sample was drawn 24 to 27 days after the second blood sample. After the blood was drawn, the samples were centrifuged and the serum drawn off. The sera then were frozen and stored at -20°C until thawed for assay.

All samples were tested either undiluted or in 2-fold serial dilutions, using Hanks Balanced Salt Solution as the diluent. When the assays were run, 0.6 mL of the diluted serum was combined with 0.6 mL of virus. Each dilution of serum (0.6 mL) was challenged with an equal volume of Type 4 adenovirus or Type 7 adenovirus, each at a concentration of approximately 100 $TCID_{50}$/ml. This combination was mixed and placed in a water bath at 37°C for 2 hours.

After the 2-hour incubation period, 0.2 mL of the mixture was inoculated into each of five tubes of human embryonic kidney tissue, each containing 1.5 mL of MEM medium with 2% fetal bovine serum. The test was placed in an incubator at 35-37°C. The test was scored for

cytopathic effects (CPE) at 14 and 21 days with a media refeed at 7 and 14 days of the test. Titers were determined by the Karber method of calculation (Mantel, 1967).

Controls for the test were: (a) Type 4 adenovirus (100 $TCID_{50}$/mL) incubated with Type 4 antiserum, (b) Type 7 adenovirus (100 $TCID_{50}$/mL) incubated with Type 7 antiserum, (c) Type 4 adenovirus (100 $TCID_{50}$/mL) incubated with Type 7 antiserum, (d) Type 7 adenovirus (100 $TCID_{50}$/mL) incubated with Type 4 antiserum, and virus alone in $\log_{10}$ dilutions, beginning with the dilution used in the test (i.e., 100 $TCID_{50}$/mL). All controls were scored for CPE at 7 and 14 days, with a media refeed at 7 days.

Analysis Procedures

Exploratory comparisons of standard parametric procedures performed with the raw data, parametric procedures applied to log-transformed data (i.e., ln(x+1)), and nonparametric analyses of raw data indicated that the analysis results were sensitive to the presence of several exceptionally high values in the distribution of antibody concentrations. The effect of these extreme values on estimates of statistical parameters was such that stronger associations were obtained with nonparametric analysis procedures, followed by parametric analyses with log-transformed antibody values, with raw antibody concentrations producing the weakest estimates of associations between antibody levels and the other study variables.

These preliminary analyses suggested that analysis procedures were needed which provided protection against the potentially misleading effects of outlier antibody values. Therefore, the data analyses reported in this paper were conducted with the log-transformed antibody values. The intermediate effect sizes obtained with the log-transformed data made these findings a reasonable compromise which retained the strengths of parametric analyses (e.g., proportion of variance explained interpretations of findings) while still controlling the influence of extreme data points.

Multivariate repeated measures analyses of variance (MANOVAs) were conducted with personality (Neurotic versus Emotionally-Stable) as a between-persons group classification and time of blood sample (two days after inoculation; one month after inoculation; two months after inoculation) as a within-subjects repeated measures factor. Two such MANOVAs were conducted, one with the three adenovirus 4 measurements as the dependent variables and one with the adenovirus 7 measures as the dependent variables. Additional correlation analyses were

performed using Pearson product moment correlations. All analyses were conducted with the SPSS^x (1988) analysis package.

Results

Check for Prior Exposure.

Detectable immunoglobulin G (IgG) neutralizing antibodies to adenovirus 4 were present after two days in 58.3% of the recruits. Detectable IgG antibodies to adenovirus 7 were present at this time for 91.7% of the recruits. Subsequent analyses, therefore, were conducted separately for those recruits with presumed prior exposure and those without for adenovirus 4.

Results for Recruits with Prior Exposure to the Viruses.

The repeated measures MANOVA produced comparable results for both adenoviruses (Table 1). The average antibody level was comparable in the two groups (Adenovirus 4, $F_{1,13} = 0.86$, $p > .371$; Adenovirus 7, $F_{1,20} = 4.00$, $p > .059$). Antibody levels increased significantly over time (Adenivorus 4, Hotelling's $T^2_{2,11} = 50.13$, $p < .001$; Adenovirus 7, Hotelling's $T^2_{2,20} = 213.47$, $p < .001$) as would be expected if the inoculations were effective. In addition, both analyses produced significant group x time interactions (Adenovirus 4, Hotelling's $T^2_{2,11} = 6.49$, $p < .014$; Adenovirus 7, Hotelling's $T^2_{2,20} = 25.88$, $p < .001$) which indicated that the profile of change in antibody levels over time was different for the two groups.

A posteriori univariate comparisons were made between the emotionally-stable recruits and the neurotic recruits to determine the basis for the group x time interaction. These comparisons indicated that emotionally-stable recruits had higher antibody levels than neurotic recruits two days after inoculation (Adenovirus 4, $t = 3.38$, $p < .016$; Adenovirus 7, $t = 6.99$, $p < .001$), but not one or two months after inoculation (absolute $t < .53$ for all tests).

Table 1
Antibody Levels as a Function of Group and Time in Previously Exposed Recruits

Virus	2-Days Post Mean	S.D.	1-Month Post Mean	S.D.	2-Months Post Mean	S.D.	Significance for Effect of: G	T	G x T
Type 4									
Stable	3.45	1.20	4.64	1.19	5.45	1.23	.371	.000	.014
Neurotic	1.74	.37	4.84	.58	5.76	1.04			
Type 7									
Stable	4.26	1.24	6.61	1.33	7.19	.79	.059	.000	.000
Neurotic	1.58	.28	6.87	.09	7.36	1.20			

NOTE: "Post" refers to the fact that the blood samples were obtained after the inoculations. "G" refers to group differences, "T" refers to changes over time, and "G x T" refers to the group by time interaction. Results are for analyses restricted to participants with detectable antibodies 2 days after inoculation (n = 22 for Type 7; n = 14 for Type 4). Antibody levels are reported as ln(Measured Antibody + 1).

The differences in antibody levels two days after inoculation translate into substantial point biserial correlations between group membership and individual differences in antibody levels (Adenovirus 4, r_{pb} = -.74; Adenovirus 7, r_{pb} = -.84). These point biserial correlations overestimate the population correlation between neuroticism and antibody levels because the selection of extreme scorers on the neuroticism dimension (cf., pp. 5-6) produces a statistical artifact known as enhancement of range (Hunter et al., 1982). To estimate the population correlations more accurately, each study participant's actual neuroticism score (rather than group membership) was correlated with antibody levels two days after inoculation and Hunter et al.'s (1982, pp. 59-64) formula to correct for enhancement of range was applied. The resulting estimates of the true population correlations between scores on Neuroticism and antibody levels two days after inoculation were r = -.39 for Adenovirus 4 and r = -.48 for Adenovirus 7.

Results for Recruits without Prior Exposure to the Viruses

The repeated measures MANOVA for those participants with no detectable antibodies to adenovirus 4 two days after inoculation (n = 10, 5 neurotic, 5 stable) showed that the two groups had comparable average antibody levels ($F_{1,8}$ = .20, p > .663) and that antibody levels increased over time (Hotelling's $T^2_{2,7}$ = 151.33, p < .001). The group x time interaction was statistically

nonsignificant (Hotelling's $T^2_{2,7} = .09$, $p > .915$), thereby indicating that the changes in antibody levels over time were comparable for the two groups.

Group Membership, Antibody Levels, and Symptom Complaints

Neurotic recruits reported more severe URI, musculoskeletal problems, and miscellaneous symptoms during the first month of basic training than emotionally-stable recruits (Table 2). In contrast, higher levels of antibodies two days after inoculation were related to less severe symptomatology in each of these three categories.

Partial correlations were computed to test two alternative models that might account for the observed patterns of correlations (Table 2). One model assumed that covariation between

Table 2

Group Membership and Day 2 Antibody Levels as Predictors of Symptom Composites

	Personality Group		Antibody Level	
	r	Partial r	r	Partial r
Adenovirus 7 (n = 18)				
URI	.26	.31	-.14	.23
Musculoskeletal	.36	.19	-.31	.04
Miscellaneous	.61	.33	-.54	.04
Adenovirus 4 (n = 12)				
URI	.27	.19	-.19	.02
Musculoskeletal	.54	.26	-.43	-.21
Miscellaneous	.60	.46	-.37	.04

NOTE: The degrees of freedom for the table differ from those in other analyses, because some subjects missed one or more illness data collection sessions. The partial correlations for each predictor are those obtained controlling for the other predictor, e.g., controlling for personality group to estimate the partial correlation between complaints and antibody level.

symptom complaints and immune status occurred because neurotic tendencies were a common cause of differences in both. If this hypothesis were correct, the partial correlations between antibody levels and symptom complaints controlling for neuroticism would be near zero. The alternative model assumed that neurotic tendencies were associated with symptom complaints because neurotic tendencies contribute to psychological processes that cause down-regulation of

the immune system under stress. If this down-regulation is the link between personality and illness and if antibody level is a suitable index of the cumulative effect of stress on the immune system, the partial correlations between neuroticism and the symptom composites controlling for antibody levels would be zero.

The distribution of the partial correlations which represented tests of the first model suggested that the true effects were near zero. These correlations ranged from r = -.21 to r = .23 with a median value of .04. In contrast, the distribution of the partial correlations to test the second model suggested that the true effects differed from zero. These correlations ranged from .19 to .46 with a median of .29. Thus, the partial correlations which would support the second model were in the small to moderate range defined by Cohen (1969). Although none of these partial correlations was statistically significant given the small sample size for the analysis, a consistent trend toward nonzero associations was evident for the second model, but not for the first model.

Discussion

This study was expected to be an investigation of the primary antibody response to vaccination because prior serological surveys suggested that few recruits would have been exposed to adenoviruses 4 and 7 prior to basic training (Foy & Grayston, 1982). The nature of the study changed when detectable antibodies to adenovirus 7 were found two days after inoculation in nearly all participants (91.7%), and IgG antibodies to adenovirus 4 were found at that time in more than half of the participants (58.3%). These results indicated that most recruits had been previously exposed to one or both adenoviruses, as antibody responses would be expected to develop more slowly if a primary exposure was being studied (Roitt et al., 1985). It is not clear why the proportion of recruits with antibodies was so much higher than expected, but it may be that the viruses in question are becoming more widespread in the population at large. In some populations, such as Taiwan and Japan, the probability of past exposure in adults was much higher than in the United States in the 1960s (Foy & Grayston, 1982). Increased international travel and other factors may have produced wider dissemination of these viruses in the United States than was the case when the prevalence estimates for these viruses that guided the study design were determined. Whatever the reason for the high frequency of exposure, it

was reasonable to regard nearly all participants as showing anamnestic responses to adenovirus 7 and more than half of the participants as showing anamnestic responses to adenovirus 4. The study, therefore, became primarily an investigation of an anamnestic immune response.

The unanticipated shift from the study of primary antibody responses to the study of anamnestic responses was serendipitous because anamnestic responses were related to neuroticism and primary antibody responses were not. The interaction between group membership and time of blood draw was statistically significant for both adenovirus 4 and 7 in those individuals previously exposed to the viruses. In contrast, the group by time interaction did not even approach statistical significance for those individuals without prior exposure to adenovirus 4. Comparisons based on significance tests are affected by differences in sample size, but the contrast between the primary and anamnestic antibody response cannot be attributed to this factor. The group by time interaction for the anamnestic responses clearly was the result of group differences in antibody levels two days after inoculation.

The present indications that stress affected the anamnestic response in neurotic individuals reinforce the link between human studies and animal studies of antibody responses initially established by Glaser et al. (1992). This reinforcement is important because animal models have been more consistent in demonstrating an influence of stress on antibody production than have human studies to date. Although early studies of stress and antibody responses in humans produced negative results (Greene et al., 1978; Locke & Heisel, 1977), the present findings demonstrate that Glaser et al.'s (1992) findings are replicable and apply to more than one type of antigen. Combined with animal studies indicating effects of stress on the anamnestic response (Cunnick et al., 1991; Moynihan, Ader, Grota, Schachtman, & Cohen, 1990; Solomon, 1969), the available evidence makes it reasonable to infer that stress does affect antibody production.

If the inference that stress affects antibody production in humans is accepted, it is reasonable to wonder why earlier studies did not demonstrate this association. One factor that may account for this recent convergence of animal and human findings may be that recent human studies have matched typical laboratory conditions reasonably closely than was true in previous studies. Both the present study and that by Glaser et al. (1992) involved living conditions and stresses that were more consistent across the study participants than they typically would be in a random sample from a human population. In the case of basic training, institutional control

over the recruits' lives results in standardized activities, comparable structuring of environmental challenges, and similar living conditions. In the case of the medical students studied by Glaser et al. (1992), routine attendance at class and the demands of preparing for examinations imply greater similarity of living conditions and psychosocial challenges than typically would be the case in a sample drawn from a less homogenous population or even the same population at a different time.

One important point of divergence between the Glaser et al. (1992) findings and the present results merits comment. Glaser et al. (1992) found that psychosocial variables were more strongly correlated to the initial antibody responses to inoculation with hepatitis B vaccine, but were not related to the anamnestic response. This potentially important difference between the studies could be the product of any of several methodological differences between the studies. These differences include differences in the viruses studied, length of time since initial exposure to the viruses, the timing of the antibody measurements relative to the inoculations, the methods of measuring neurotic tendencies, and the analysis procedures. Further study is needed to systematically evaluate the significance of these various differences for the results obtained.

The effects of stress on the anamnestic response of neurotic individuals probably did not affect their health during training. Even though higher antibody levels two days after inoculation were associated with reporting fewer or less severe symptoms during the following month of basic training, the associations may not reflect an influence of lower anamnestic response on objective health status. One reason for skepticism is the ordering of the magnitudes of the correlations for different symptom composites. The association was strongest when antibody levels were related to miscellaneous symptom reporting, followed by musculoskeletal complaints, with URI the weakest correlate. The same ordering of correlations occurred for neuroticism, a personality variable which appears to produce complaints independent of underlying pathology in many types of illness (Costa & McCrae, 1987). The associations between neuroticism and symptom reporting are so reliable that hypochondriacal tendencies often are included in the definition of neuroticism constructs (e.g., Watson & Pennebaker, 1989). Coupling this fact with the present correlation between neuroticism and antibody levels, the observed antibody-symptom complaints correlations could be the product of the influence of neurotic tendencies on both of these health-relevant outcomes. The partial correlation analyses which showed that antibody

levels and symptom composites were completely independent on the average after controlling for neuroticism supported this interpretation of the data.

The evidence for a model which assumes that the correlations between antibody levels and symptom composites were spurious is not conclusive at this time. Other models could produce the data reported here. For example, the same pattern of findings could occur if an impaired anamnestic response was only one of several aspects of immune function which was affected by stress and if down-regulation of the immune system manifested itself as a more severe flu-like syndrome including muculoskeletal and gastrointestinal symptoms rather than just respiratory symptoms when infected by a virus. If these conditions held, neuroticism could be more strongly related to symptom composites than antibody levels were because neuroticism was linked to outcomes by several pathways. The magnitudes of the associations to symptoms would be explained by the fact that down-regulation had a stronger causal impact on relatively severe symptomatic expressions of illness. The stress of training appears to down-regulate at least one other element of immune resistance to viral illness, natural killer cell activity (Vickers, Hervig, Levy, et al., in preparation), so this alternative model has some plausibility.

The observed pattern of associations between individual differences in stress susceptibility, down-regulation of antibody production, and illness may be affected by the situational context of the study. The typical recruit in basic training encounters many viruses. Some of these viruses are likely to be ones that have not been encountered before, and these viruses are likely to be the predominant factors in respiratory illness in basic training. The perturbations of the immune system reflected in the down-regulation of the anamnestic antibody response may have more impact on health in situations when challenges to the immune system are less substantial.

In summary, the present findings reinforced Glaser, et al's (1992) demonstration of stress-related down-regulation of antibody production in humans, but suggested that this down-regulation may have no effect on health. The contrast between these recent findings and older reports of no down-regulation may be the result of differences in contextual factors such as the timing of stress and degree of matching of living and working circumstances. Such contextual factors also may have contributed to the present finding that down-regulation of antibody production apparently did not affect health. The overall import of the present study, therefore, is that investigations of stress-related down-regulation of antibody production in humans should

be a productive component of psychoimmunological research, but study designs must be sensitive to the need to test plausible alternative models of the interplay of stress, antibody formation, and illness.

References

Bourne, P. G. (1967). Some observations on the psychosocial phenomena seen in basic training Psychiatry, 30, 187-196.

Coe, C. L., Rosenberg, L. T., Rischer, M., & Levine, S. (1987). Psychological factors capable of preventing the inhibition of antibody responses in separated infant monkeys. Child Development, 58, 1420-1430.

Cohen, J. (1969). Statistical power analysis for the social sciences. NY: Academic Press.

Costa, P. T., Jr., & McCrae, R.R. (1985). NEO Personality Inventory Manual. Odessa, FL: Psychological Assessment Resources.

Costa, P. T., Jr., & McCrae, R. R. (1987). Neuroticism, somatic complaints, and disease: Is the bark worse than the bite? Journal of Personality, 55,299-316.

Costa, P. T., Jr., & McCrae, R. R. (1988). Personality in adulthood: A six-year longitudinal study of self-reports and spouse ratings on the NEO Personality Inventory. Journal of Personality and Social Psychology, 54, 853-863.

Cunnick, J. E., Cohen, S., Rabin, B. S., Carpenter, A. B., Manuck, S. B., & Kaplan, J. R. (1991). Alterations in specific antibody production due to rank and social instability. Brain, Behavior, and Immunity, 5, 357-369.

Datel, W. E., & Engle, E. O. (1966). Affect levels in another platoon of basic trainees. Psychological Reports, 19, 407-412.

Datel, W. E., Engle, E. O., & Barba, M. A. (1966). Affect levels in a company of basic trainees. Psychological Reports, 19, 903-909.

Foy, H. M., & Grayston, J. T. (1982). Adenoviruses. In A.S. Evans (Ed.), Viral infections of humans: Epidemiology and control (pp. 67-84). NY: Plenum.

Glaser, R., Kiecolt-Glaser, J. K., Bonneau, R. H., Malarkey, W., Kennedy, S., & Hughes, J. (1992). Stress-induced modulation of the immune response to recombinant hepatitis B vaccine. Psychosomatic Medicine, 54. 22-29.

Greene, W. A., Betts, R. F., Ochitill, H. N., Iker, H. P., & Douglas, R.G. (1978). Psychosocial factors and immunity: Preliminary report. Psychosomatic Medicine, 40, 87.

Hough, L. M. (Ed.) (1988). Literature review: Utility of temperament, biodata, and interest assessment for predicting job performance (ARI Research Note 88-02). Alexandria, VA: U.S. Army Institute for the Behavioral and Social Sciences.

Hunter, J. E., Schmidt, F. L., & Jackson, G. B. (1982). Meta-analysis: Cumulating research findings across studies. Beverly Hills, CA: Sage.

Janis, I. L. (1945). Psychodynamic aspects of adjustments to Army life. Psychiatry, 8, 159-176.

Jemmott, J. B., III, & Locke, S. E. (1984). Psychosocial factors, immunologic mediation, and human susceptibility to infectious disease: How much do we know? Psychological Bulletin, 95, 78-108.

LaRocco, J. M., Ryman, D. H., & Biersner, R. J. (1977). Life history and mood as predictors of adjustment in Navy recruit training. Journal of Community Psychology, 5, 46-51.

Laudenslager, M. L., Fleshner, M., Hofstadter, P., Held, P. E., Simons, L., & Maier, S. F. (1988). Suppression of specific antibody production by inescapable shock: Stability under varying conditions. Brain, Behavior, and Immunity, 2, 92-101.

Lazarus, R. S., & Folkman, S. (1984). Stress, appraisal, and coping. NY: Springer-Verlag.

Locke, S. E., & Heisel, J. S. (1977). The influence of stress and emotions on the human immune response. Biofeedback and Self-Regulation, 2, 320.

Mantel, N. (1967). Adaptation of Karber's method for estimating the exponential parameter from quantal data and its relationship to birth, death, and branching process. Biometrics, 23, 739-746.

Maskin, M. H., & Altman, L. L. (1943). Military psychodynamics: Psychological factors in the transition from civilian to soldier. Psychiatry, 6, 263-269.

McCrae, R. R., & Costa, P. T., Jr. (1985). Comparison of EPI and psychoticism scales with measures of the five-factor model of personality. Personality and Individual Differences, 6, 587-597.

Moynihan, J. A., Ader, R., Grota, L. J., Schachtman, T. R., & Cohen, N. (1990). The effects of stress on the development of immunologial memory folliwing low-dose antigen priming in mice. Brain, Behavior, and Immunity, 4, 1-12.

O'Leary, A. (1990). Stress, emotion, and human immune function. Psychological Bulletin, 108, 363-382.

Roitt, I. M., Brostoff, J., & Male, D. K. (1985). Immunology (pp. 8.1-8.10). St. Louis: Mosby.

Rose, R. M., Poe, R. O., & Mason, J. W. (1968). Psychological state and body size as determinants of 17-OHCS excretion. Archives of Internal Medicine, 121, 406-413.

Solomon, G. F. (1969). Stress and antibody response in rats. International Archives of Allergy, 35, 97-104.

SPSS, Inc. (1988). SPSS-X users guide. 3rd edition. Chicago: SPSS, Inc.

Thoits, P. A. (1984). Coping, social support, and psychological outcomes: The central role of emotion. In P. Shaver (Ed.), Review of personality and social psychology, (Vol. 5, pp. 219-238). Beverly Hills, CA:Sage.

Vickers, R. R., Jr., & Hervig, L. K. (1988a). Psychosocial risk factors for upper respiratory infections: Assessment of upper respiratory illness during basic training. (NHRC Report 88-23). San Diego, CA: Naval Health Research Center.

Vickers, R. R., Jr., & Hervig, L. K. (1988b). Psychosocial risk factors for upper respiratory infections: Personality predictors of URI during basic training. (NHRC Report 88-36). San Diego, CA: Naval Health Research Center.

Vickers, R. R., Jr., Hervig, L. K., Levy, S. M., Herberman, R.B., & Whiteside, T.L. (in preparation). Psychological correlates of natural killer cell activity in military recruits. San Diego, CA: Naval Health Research Center.

Vickers, R. R., Jr., Hervig, L. K., Wallick, M. T., Poland, R. E., & Rubin, R. T. (1987). Psychological correlates of cortisol excretion in normal individuals under stress. (NHRC Report 87-1). San Diego, CA: Naval Health Research Center.

Vickers, R. R., Jr., Kolar, D. W., & Hervig, L. K. (1989). Personality correlates of coping with military basic training. (NHRC Report 89-3). San Diego, CA: Naval Health Research Center.

Vickers, R. R., Jr., Kusulas, J. W., & Hervig, L. K. (in preparation). Positive affectivity and negative affectivity: A comprehensive model for personality-mood associations? San Diego, CA: Naval Health Research Center.

Voors, A. W., Rytel, M. W., Jenkins, C. D., Pierce, W. E., & Stewart, G. T. (1969). Prediction of sickness in naval recruits by Minnesota Multiphasic Personality Inventory scores. American Review of Respiratory Disease, 99, 420-425.

Watson, D., & Pennebaker, J. W. (1989). Health complaints, stress, and distress: Exploring the central role of negative affectivity. Psychological Review, 96, 234-254.

Zurcher, L. A., Jr. (1968). The naval recruit training center; A study of role assimilation in a total institution. Sociological Inquiry, 31, 85-98.

REPORT DOCUMENTATION PAGE

1a. REPORT SECURITY CLASSIFICATION Unclassified	1b. RESTRICTIVE MARKINGS N/A
2a. SECURITY CLASSIFICATION AUTHORITY N/A	3. DISTRIBUTION/AVAILABILITY OF REPORT Approved for public release; distribution unlimited.
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE N/A	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) Report No. 91-47	5. MONITORING ORGANIZATION REPORT NUMBER(S)

6a. NAME OF PERFORMING ORGANIZATION Naval Health Research Center	6b. OFFICE SYMBOL (*If applicable*) 232	7a. NAME OF MONITORING ORGANIZATION Chief, Bureau of Medicine and Surgery
6c. ADDRESS (*City, State, and ZIP Code*) P. O. Box 85122 San Diego, CA 92186-5122		7b. ADDRESS (*City, State, and ZIP Code*) Navy Department Washington, DC 20372-5120
8a. NAME OF FUNDING/SPONSORING ORGANIZATION Naval Medical Research & Development Command	8b. OFFICE SYMBOL (*If applicable*)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER ONR Reimbursable
8c. ADDRESS (*City, State, and ZIP Code*) NNMC Bethesda, MD 20889-5044		10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
61153N	MR04101	00A	6004

11. TITLE (*Include Security Classification*)
(U) Neuroticism and Antibody Responses in Military Recruits

12. PERSONAL AUTHOR(S)
Vickers, Jr., Ross R., Hervig, Linda K., Rappaport, Ruth, and Linard, Paul

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (*Year, Month, Day*)	15. PAGE COUNT
interim	FROM _____ TO _____	1991 September 12	20

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (*Continue on reverse if necessary and identify by block number*)
FIELD	GROUP	SUB-GROUP	antibody response; psychological stress; adenovirus; personality; military recruit; neuroticism

19. ABSTRACT (*Continue on reverse if necessary and identify by block number*)

(U) The hypothesis that neurotic individuals produce lower levels of antibodies under stress than emotionally-stable individuals was tested by measuring neutralizing antibody responses to inoculations for adenoviruses 4 and 7 in military recruits (n = 24) during basic training. Among recruits with prior exposure to the viruses, neurotic individuals had significantly lower levels of antibody to both viruses two days after inoculation, but not four weeks and eight weeks after inoculation. Among recruits with no prior exposure, there were no significant group differences. Neurotic recruits also reported more severe respiratory symptoms, but individual differences in antibody responses were weak predictors of differences in illness. Down-regulation of antibody formation apparently occurred in neurotic recruits, but the magnitude and duration of the effect were not sufficient to produce substantial health consequences in this setting.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (*Include Area Code*)	22c. OFFICE SYMBOL
Ross R. Vickers, Jr.,	(619) 553-8454	232

☆U.S. Government Printing Office: 1985—507-047